

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Peter S. Lu et al.

Application No.: 10/663,538

Filed: September 15, 2003

For: NUCLEIC ACID MOLECULE
ENCODING A CLASP-2
TRANSMEMBRANE PROTEIN
(PREVIOUSLY CLASP PROTEINS)

Customer No.: 20350

Confirmation No. 5609

Examiner: Bridget S. Bunner

Technology Center/Art Unit: 1647

**DECLARATION UNDER 37 C.F.R.
§1.132 OF DR. PETER S. LU**

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Peter S. Lu, state as follows:

2. I received a M.D. degree from University of Washington Medical School, M.S. degree from University of Washington, and B.S. degree from California Institute of Technology. Currently I am the Chief Executive Officer and President of Arbor Vita Corporation. I founded this company in 1998. I am also a named inventor for the above-identified patent application. A copy of my curriculum vitae is attached hereto as **Exhibit 1**.

3. I have read and am familiar with the contents of this patent application. In addition, I have read the Office Action mailed October 17, 2007, received in the present case. I understand the Examiner has questioned whether the claimed CLASP-2 nucleic acids have utility. Although the Examiner acknowledges that CLASP-2 expression levels decrease at 1 hour, 2 hours, and 4 hours after T cell activation (pg 125, lines 4-14), the Examiner questions whether this is a significant decrease as compared to T-cells that have not been activated.

4. This declaration is provided to establish the significance of the decrease in CLASP-2 expression.

5. Original Figure 14 of the application (now renumbered as Figure 11) shows how CLASP-2 expression in T-cells decreases after activation, for example at 1, 2 and 4 hours after activation.

6. The first sample taken at 0 hours post activation in Figure 14 indicates the level of CLASP-2 mRNA in unactivated T cells - this level is higher than CLASP-2 levels at 1 and 2 hours post-activation.

7. Original Figure 14 of the application (now renumbered as Figure 11) incorporated various controls to establish the significance of decreased CLASP-2 expression seen upon activation. As explained in the specification (Example 9, page 124, lines 4-8), cellular mRNA taken from T cells before and after activation was adjusted to ensure that equal amounts of total RNA were loaded onto the gel. In addition, "[e]ven gel loading was monitored by ethidium bromide staining" of the gel. Paragraph 482 of the published application.

8. The uniform, even intensities of the 28S rRNA bands at 0, 1, 2 and 4 hours post activation in Figure 14A, confirm that the decrease in CLASP-2 expression was specific for CLASP-2 alone, and was not seen for other mRNA.

9. Because decreased expression after activation is seen only for CLASP-2 and not for all RNA in general, the decreased expression is significant.

10. Exhibit 2 shows the expression of a similar but distinct gene (CLASP-1) at various hours post-activation. As seen, levels of CLASP-1 mRNA did not show a decrease and 1 and 2 hours post activation. In fact, the levels were seen to increase slightly instead. Thus, the data in Exhibit 2 confirms that the decreased expression of CLASP-2 is significant and specific to CLASP-2 alone.

11. I conclude that the decreased expression of CLASP-2 upon T-cell activation is significant because no similar decrease in expression was seen after activation, either for RNA in general or more specifically for similar genes such as CLASP-1.

12. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 4-16-08

By: E. A. L.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Lu, Peter Sin-yi	POSITION TITLE President/CEO		
eRA COMMONS USER NAME PETERLU			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
California Institute of Technology	B.S.	1977	Biology
University of Washington	M.S.	1980	Microbiology/ Immunology
University of Washington Medical School	M.D.	1988	Medicine

A. Positions and honors.

Positions and Employment

- 1988-1989 Medical intern, Internal Medicine; University of Washington Medical School
 1989-1994 Resident and research fellow, Department of Dermatology; Stanford University
 1992-1998 Post-Doctoral fellow, Howard Hughes Medical Institute; Stanford University
 1992-1998 Clinical Instructor, Attending, Psoriasis Day Care Center, Department of Dermatology, Stanford Medical School
 1995-present Director, Stanford Papua New Guinea Medical Project
 1998-present Founder, President, CEO, Arbor Vita Corporation
 2002-present Medical Director, Community Pregnancy Center, STD clinic

Research Experience and Appointments

- 1974-1976 Mechanism of antibody diversity; California Institute of Technology; advisor Leroy Hood, M.D./Ph.D.
 1977-1978 Gene regulation in development; California Institute of Technology; advisor Eric Davidson, Ph.D.
 1978-1981 Role of idiotypic network in tumor immunity; University of Washington; advisor Robert Nowinski, Ph.D.
 1981-1984 Eukaryotic gene regulation; University of Washington; advisor Harold Weintraub, M.D./Ph.D.
 1992-1998 Adhesion molecules in T cell activation; Howard Hughes Medical Institute, Stanford University; advisor Mark M. Davis, Ph.D.

Honors

- 1988 Alpha Omega Alpha, University of Washington
 1991 Resident Teaching Award, Stanford Medical School
 1991 Paul H. Jacobs Award, Stanford Medical School

B. Patent applications and peer-reviewed publications (in chronological order).

Dr. Lu is an inventor on 5 granted patents and has over 80 patent applications. Dr. Lu has five peer-reviewed publications and several presentations/posters presented at international conferences.

Granted Patents:

- AU 62854/99 - Cadherin Like Asymmetry Protein-1 and methods for use
 US 6,565,848 - Cadherin Like Asymmetry Protein-1 and methods for use
 US 6,942,981 - Molecular Interactions in Hematopoietic Cells

US 7,312,041- Methods of Diagnosing Cervical Cancer
 US 7,312,071 B2- Effective Monitoring System for Anthrax, Smallpox, or Other Pathogens

Example Patent applications that have published include:

<u>Title</u>	<u>Publication No.</u>
CLASP-2 Transmembrane Protein	W00061747
Molecular Interactions in Hematopoietic Cells	W00069896
Molecular Interactions in T Lymphocytes	W00069897
Molecular Interactions in Allergy	W00069898
CLASP-3 Transmembrane Protein	W001042297
CLASP-7 Transmembrane Protein	W00142295
CLASP-4 Transmembrane Protein	W00142294
CLASP-5 Transmembrane Protein	W00142296
CLASP-7 Transmembrane Protein	20020169283
CLASP-5 Transmembrane Protein	20020102267
CLASP-4 Transmembrane Protein	20020068302
CLASP-3 Transmembrane Protein	20020086382
CLASP-1 Transmembrane Protein	W00185908
Molecular Interaction in Hematopoietic Cells	W00231512
CLASP Membrane Proteins	20030103992
Molecular Interactions in Hematopoietic Cells	W00242422
PDZ Domain Interactions and Lipid Rafts	W002066954
PDZ Domain Interactions and Lipid Rafts	20030049695
Molecular Interactions in Cells	W003014303
CLASP Membrane Proteins	W003025120
Effective Monitoring System for Anthrax, Smallpox, of Other Pathogens	20030153021
Methods of Diagnosing Cervical Cancer	20040018487
Methods of Diagnosing Cervical Cancer	WO2004/022006A2
Molecular Interactions in Neurons	WO2004045535
Methods of Treating Cervical Cancer	20040229298A1
Methods and Compositions for Treating Cervical Cancer	WO2004/076646
Modulation of MUC1 Mediated Signal Transduction	WO2004/092339A2

Publications include:

Y. Murata, C.B. Martin, T. Ikenoue, **P.S. Lu**. (1978). Antepartum Evaluation of the Pre-ejection Period of the Fetal Cardiac Cycle. Am. J. Ob/Gyn. 132: 278-284.

S. Kindel, **P.S. Lu**, B. Smoller. (1994). Intravascular Crystals Provide a Diagnostic Clue in the Diagnosis of Monoclonal Cryoglobulinemia. J. Eur. Acad. Dermatol. Venereol. 3: 185-188.

E.J. Messika, **P.S. Lu**, Y.J. Sung, T. Yao, J.T. Chi, Y.H. Chien, M.M. Davis. (1998). Differential Effect of B Lymphocyte-induced Maturation Protein (Blimp-1) Expression on Cell Fate During B Cell Development. J. Exp. Med. 188: 135-146

P.S. Lu. (2006). Early Diagnosis of Avian Influenza. Science. 312: vol.5772, p.337.

H. Cui, A. Hayashi, H.S. Sun, M.P. Belmares, C. Cobey, T. Phan, J. Schweizer, M.W. Salter, Y.T. Wang, R.A. Tasker, D. Garman, J. Rabinowitz, **P.S. Lu**, M. Tymianski. (2007). PDZ Protein Interactions Underlying NMDA Receptor-mediated Excitotoxicity and Neuroprotection by PSD-95 Inhibitors. J. Neurosci. 27: 9901-15.

Representative posters/presentations include:

J.G. Schweizer, L. Liu, C.W. Mahoney, J. Silver, M.G. Berard-Bergery, Y. A. Labiad, R. Peck, M. Belmares, A. Bisht, T. Ho, H. Li, L. Peysakhovich, C. Somoza, C. Tan, B. Weigl, J. Sellors, **P.S. Lu**. Development of a Rapid Diagnostic Strip Test for Cervical Pre-Cancer and Cancer. 24th International Papillomavirus Conference, Beijing, China (2007).

A. Abate, M. Urtiaga, L. Peysakhovich, V. Chockalingam, H. Li, J. Silver, **P.S. Lu**, J.G. Schweizer, C. Somoza. MAGI1 Protein Degradation in Hela Cells Is Restored by C-terminal HPV16-E6 Peptide. 24th International Papillomavirus Conference, Beijing, China (2007).

J.W. Sellors, J.G. Schweizer, C.W. Mahoney, L. Liu, Y.A. Labiad, M.G. Berard-Bergery, C. Tan, R. Sankaranarayanan, Y.L. Qiao, B. Weigl, R. Peck, **P.S. Lu**, Y. Bao, K. Deodhar, B.M. Nene. Validity of E6 Oncoprotein as a Marker for Risk of Progression: Prospective Studies in China and India. 24th International Papillomavirus Conference, Beijing, China (2007).

J.W. Sellors, J.G. Schweizer, **P.S. Lu**, B. Weigl, R. Peck, L. Liu, C.W. Mahoney, Y.A. Labiad, M.G. Berard-Bergery, C.Tan, Y.L. Qiao, W. Chen, K. Deodhar, B.M. Nene. Performance of an E6 Strip Test for Primary Screening of Cervical Cancer. 24th International Papillomavirus Conference, Beijing, China (2007).

J.G. Schweizer, R. Peck, J.Silver, C. Somoza, B. Weigl, R. Sankaranarayanan, Y. Qiao, **P.S. Lu**, J. Sellors. Development of a HPV-E6 Oncoprotein-Based Rapid Strip Test for Cervical Intraepithelial Neoplasia. ISSTD Conference, Seattle, Washington (2007).

J.W. Sellors, B. Weigl, R. Peck, P. Eder, J.G. Schweizer, **P.S. Lu**, A. Lorincz, K. Deodhar, R. Sankaranarayanan, Y. Qiao. HPV Screening Test Development for Low-Resource Settings, ISSTD Conference, Seattle, Washington (2007).

Somoza, C., Bagowski C.P., Peysakhovich, L., Mahoney, S., Khanna, R., Lynch, C., Silver, J., **Lu, P.S.**, Schweizer, J.G. High-risk HPV-E6 activates the oncogenic JNK pathway by interacting with PDZ-protein Magi-1. 23rd International Papillomavirus Conference, Prague, Czech Republic (2006).

C. Research support.

Ongoing Research Support

2 R44 CA 121155-02 Lu, Peter S. (PI) 8/31/06- 5/31/08

NCI

A Novel Diagnostic Assay for Oncogenic Human Papillomaviruses

The specific aim of the project was to a) expand our monoclonal antibody detection cocktail to include all 20 known high-risk types of HPV, b) optimize the quantification of HPV-E6 oncoprotein in cytology samples and correlate their levels with the stage of transformation, c) extend the studies correlating high-risk HPV-E6 oncoprotein levels with cytological stages by optimizing assay sensitivity with cytology samples, establishing sample collection and storage conditions, and begin validating the assay with more than 1,000 cytology samples of diverse geographic origin.

Role: PI

Completed Research Support

1 R43 AI068160-01 Schweizer (PI) 03/15/06-02/28/08

NIH/NIAID

Rapid Strip Test for Cervical Cancer via HPV-E6 Detection

The specific aim of the project was to a) Select anti-E6 antibodies/oncogenic E6 capture (PDZ) reagents for individual lateral flow-based assays for HPV types 16, 18, 31, 33, 45, 52, and 58 with a sensitivity better than 2ng recombinant E6, b) determine optimal detection system and conditions for a lateral flow-based assay to achieve a sensitivity of 10-50pg recombinant E6, c) determine optimal conditions for sample storage and processing for a lateral flow assay based cervical cancer assay, and d) demonstrate a proof-of-principle multiplexed lateral flow assay for all 7 HPV types by combining PDZ capture and anti-E6 mAb for all HPV types on a single strip.

Role: Advisor

1 R43 NS046954-01 A1 Lu (PI) 12/15/04-05/31/05

NIH/NINDS

A Novel Drug to Reduce Neronal Damage Following Stroke

The specific aim of the project was to a) Identify the human PDZ domain-containing proteins bound by NMDA Receptors 2A, 2B, 2C, 2D, Tat-NR2B9 and a NMDA receptor 1 isoform, b) determine PDZ domain containing proteins bound by the internal PDZ ligand of nNOS, c) determine the half maximal inhibition of Tat-NR2B9 against PSD-95/NMDA R2 interactions, nNOS/PSD-95 interactions, and NMDA R/other strong PDZ interactions as a reference, and d) identify specific peptide inhibitors of PSD-95 domain 1 and 2 that are more selective than Tat-NR2B9.

Role: PI

1 R43 CA103383-01 Lu (PI) 04/22/03-07/30/03

NIH/NCI

A Novel Diagnostic for Oncogenic HPV

The specific aim of the project was to a) Engineer a PDZ-domain detector and demonstrate that it specifically recognizes oncogenic HPV proteins in vitro, b) demonstrate that the PDZ-detector can recognize transfected E6 oncoproteins, and c) demonstrate selective detection of endogenous E6 protein from cervical cancer cell lines.

Role: PI

1 R43 CA099368-01 Lu (PI) 11/01/02-03/28/03

NIH/NCI

Prevention and Treatment of Cervical Cancer

The specific aim of the project was to a) determine all interactions of high-risk HPV-E6 with human PDZ domain proteins, and b) validate the interaction of high-risk HPV-E6 with PDZ domain proteins as a physiological target for a potential anti cervical cancer therapeutics.

Role: PI

1 R43 AI45274-01A2 Lu (PI) 08/01/01-01/31/02

NIH/NIAID

A Novel Family of Lymphocyte Adhesion Molecules

Role: PI

Human CLASP-1 expression in T cells upon activation

